New Biotechnology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

New Biotechnology

journal homepage: www.elsevier.com/locate/nbt

Modeling neurodegenerative diseases with patient-derived induced pluripotent cells: Possibilities and challenges

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
IPSC
Neurodegeneration
Disease models
Alzheimer's disease
Frontotemporal dementia
Ataxia
3D neural cultures
2D neural cultures

ABSTRACT

The rising prevalence of progressive neurodegenerative diseases coupled with increasing longevity poses an economic burden at individual and societal levels. There is currently no effective cure for the majority of neurodegenerative diseases and disease-affected tissues from patients have been difficult to obtain for research and drug discovery in pre-clinical settings. While the use of animal models has contributed invaluable mechanistic insights and potential therapeutic targets, the translational value of animal models could be further enhanced when combined with *in vitro* models derived from patient-specific induced pluripotent stem cells (iPSCs) and isogenic controls generated using CRISPR-Cas9 mediated genome editing. The iPSCs are self-renewable and capable of being differentiated into the cell types affected by the diseases. These *in vitro* models based on patient-derived iPSCs provide the opportunity to model disease development, uncover novel mechanisms and test potential therapeutics. Here we review findings from iPSC-based modeling of selected neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia and spinocerebellar ataxia. Furthermore, we discuss the possibilities of generating three-dimensional (3D) models using the iPSCs-derived cells and compare their advantages and disadvantages to conventional two-dimensional (2D) models.

Contents

1. Introduction

Neurodegenerative diseases (NDs) are generally described as pathological conditions in which primarily neurons degenerate and lose their functionality. Such loss of functionality results in apoptosis and culminates in severe atrophy of the affected patient brain regions. Pathogenesis of these diseases is complex and the

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http://dx.doi.org/10.1016/j.nbt.2017.05.009
1871-6784/

underlying mechanisms remain to be elucidated. The generation of patient-specific induced pluripotent stem cells (iPSC) has opened up the possibility to generate *in vitro* disease models, which can at least in theory be differentiated into any given cell type and offer the possibility to model disease *in vitro* using patient-derived cells. Over the past decade, several patient-specific iPSCs have been employed to model NDs. Despite the differences in clinical symptoms and neuropathology among these NDs, many of the impaired cellular functions are similarly affected. This makes these models not only appealing in terms of understanding early pathology before the onset of symptoms in specific diseases but also offers the opportunity to identify modes of intervention, which could be beneficial in a variety of NDs. Moreover, the advent of the CRISPR-Cas9 gene technology has improved the efficiency of genome editing and accelerated the generation of isogenic controls that retain the genetic background of the patients (Fig. 1) and makes precise genotype and phenotype correlations possible. Previous comparative studies between patient and control neurons have revealed some cellular alterations, which could be linked to mutations present in the patients. However, some of the late stage hallmarks of NDs, such as amyloid plaques and tau tangles in AD, are yet to be recapitulated in the patient-derived iPSC models [1–6]. The lack of some late stage phenotypes could possibly be due to the simplicity of the current neuron-centric models and limited cell culture period. The development of NDs typically encompasses several cell types, and a more complex, multi-cellular system may be required to capture the disease phenotypes. Furthermore, the transition from 2D to 3D culture systems has emerged in recent years with the goal of incorporating multiple cell types to better mimic the *in vivo* milieu. A discussion of the major advantages and disadvantages of these culture systems is provided at the end of this review.

2. Alzheimer's disease iPSC models

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disease and is considered the most common form of dementia, accounting for 60%-70% of all cases (World Health Organization, 2015). It is characterized by a progressive loss of cognitive and executive function abilities [7]. Approximately 44 million people worldwide are diagnosed with AD or a related dementia, and this number is expected to double every 20 years with the increase in aging population and life expectancy (Alzheimer's Disease International, 2010 & 2016). AD has become a global economic burden and continuous efforts are being made towards effective interventions to prevent, delay, and treat AD.

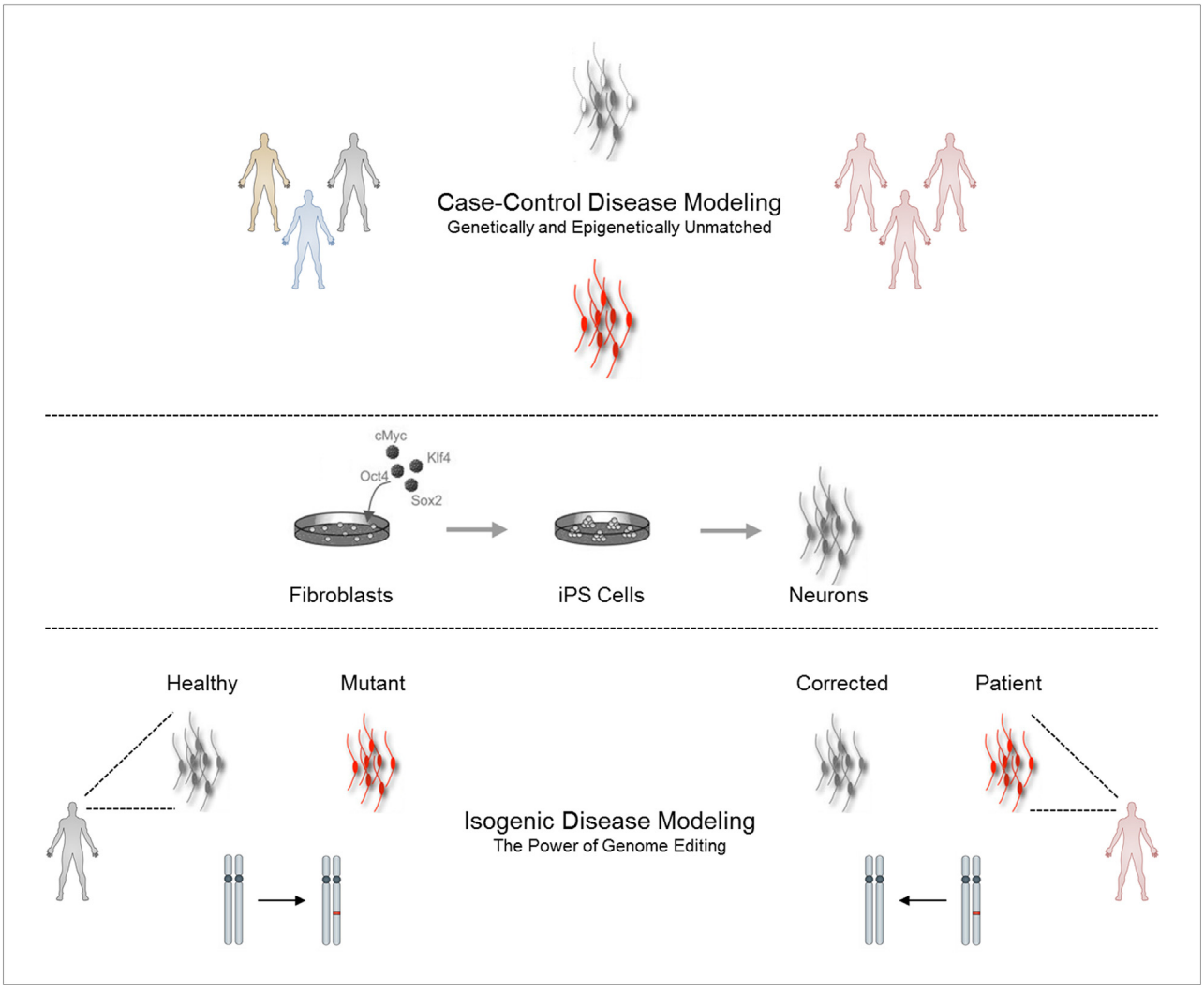

Fig 1. Illustration of the advantages in using gene edited isogenic controls for disease modeling. In the top row, patients and controls are only age- and gender- matched but may differ significantly in genetic background and epigenetic makeup compared to the patients. In contrast, a gene-edited isogenic control (bottom row) only differs from the patient at the site of mutation and comparison between the two lines is ideal for the identification of pathologies and underlying mechanisms caused by a specific mutation.

Please cite this article in press as: A. Poon, et al., Modeling neurodegenerative diseases with patient-derived induced pluripotent cells: Possibilities and challenges, New Biotechnol. (2017), http://dx.doi.org/10.1016/j.nbt.2017.05.009